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09/749,025	12/27/2000	Petrus Johannes Maria Nuijten	99511 US	6121

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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/749,025	Applicant(s) NUIJTEN ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-11,14 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11,14 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

FINAL ACTION

1. Applicant's amendment and response filed April 15, 2003 is acknowledged. Claim 6 has been canceled. Claims 7 and 14 have been amended. Claim 19 had been added.

Objection/Rejections Withdrawn

2. In view of Applicant's response the following rejections are withdrawn:

a) Objection to claim 9, paragraph 8, page 10 of the previous Office action.

b) All rejections of claim 6 are moot in view of Applicant's amendment canceling claim 6.

c) Rejection under 35 U.S.C. 102(b) of claims 7-8, paragraph 6, pages 4-7 of the previous Office action.

d) Rejection under 35 U.S.C. 102(b) of claims 14 and 17-18, paragraph 7, pages 7-10 of the previous Office action.

e) Rejection under 35 U.S.C. 112, first paragraph of claim 7, paragraph 9, pages 10-11 of the previous Office action.

f) Rejection under 35 U.S.C. 112, first paragraph of claim 14, paragraph 10, pages 11-12 of the previous Office action.

g) Rejection under 35 U.S.C. 112, first second of claim 7, paragraph 11, pages 13 of the previous Office action.

h) Rejection under 35 U.S.C. 112, first second of claim 14, paragraph 12, pages 13 of the previous Office action.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 7-11, 14 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine composition for the protection against Salmonellosis comprising an immunologically effective amount of a *Salmonella typhimurium* STMP mutated bacterium and a pharmaceutical acceptable carrier, wherein the mutated bacterium lacking flagellin does not reasonably provide enablement for a vaccine composition for the protection against Salmonellosis comprising an immunologically effective amount of any *Salmonella* mutated bacterium wherein the mutated bacterium lacking flagellin and wherein the mutated bacterium is attenuated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification has not provided enablement for: A) a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritditis, cholerasuis, dublin, abortus-ovi, abortus-equi, derby, habar, heidelberg, agona, arizonae, typhi and paratyphi* A and B wherein said mutated bacterium lacking flagellin and wherein the vaccine is protective, B) a vaccine

comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritditis, cholerasuis, dublin, abortus-ovi, abortus-equi, derby, habar, heidelberg, agona, arizonae, typhi and paratyphi A and B,* wherein said mutated bacterium lacking flagellin and wherein the mutated bacterium is attenuated.

The claims are drawn to a vaccine composition. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to *Salmonella* infection or disease induction. The specification teaches that current *Salmonella* vaccines are efficacious however they share a serious disadvantage because they generally induce an antibody population that equals that of an infection with wildtype bacteria because they possess the same antigenic load as the wildtype bacterium. The specification teaches that analysis of antibodies in the serum of *Salmonella*-positive animal does not reveal why the animal is positive, this can be due to vaccination or caused by infection with a virulent strain (page 4). The specification teaches that it would be advantages to have a so-called marker-vaccine comprising an antibody panel that differs from that of the wildtype infection and therefore the host would not make antibodies against the marker (i.e. protein) after vaccination (page 4). The specification teaches that the bacteria is no longer capable of inducing antibodies against at least one antigenic determinant of flagellin or flagella and are considered to be bacteria that do not comprise flagellin or flagella but still possesses all the antigenic determinants (page 6). Example 3 (Experiment 1) of the specification teaches that broilers were inoculated orally, subcutaneously and intramuscularly with a vaccine comprising a wild-type flagellated (fla+) *S. typhimurium* (STMP), a vaccine comprising

non-flagellated (fla-) *S. typhimurium (STM2000)* or a vaccine comprising wild-type *S. typhimurium*. The results of this experiment show that 8 out of 10 animals given the wildtype vaccine died and the surviving two had swollen livers with necrotic foci, swollen spleen and pericardial edema. One of the STMP inoculated chickens had a slight swollen liver and one of the STM2000 inoculated chickens had a slightly swollen spleen. No further abnormalities were note in the STMP or the STM2000 inoculated groups. Example 3, (Experiment 2) of the specification teaches a vaccine comprising a wild-type flagellated (fla+) *S. typhimurium* (STMP) and a vaccine comprising non-flagellated (fla-) *S. typhimurium (STM2000)* both administered orally into broilers followed by challenge infection with wild-type *S. typhimurium*. The results of the experiment show that a larger proportion of the chickens in the STMP inoculated group was culture positive after direct plating indicates that this strain colonizes the intestinal tract in higher numbers than the STM2000 strain. Example 4 of the specification teaches that pigs were inoculated orally with STMP or STM2000 followed by an oral challenge infection with wild-type *S. typhimurium*. The results of this experiment in Table 5 show that both vaccine strains were able to reduce fecal shedding of the challenge strain significantly.

The teachings of the prior art regarding *Salmonella* nonflagellated mutants are cited below:

Lockman et al *(Infection and Immunity, January 1990, p. 137-143)* teach nonflagelated mutants of *Salmonella typhimurium* (see the Title). Lockman et al teach that flagella enable bacterial cells to move chemotactically in response to stimuli and

there is evidence that these organelles function in the attachment of certain bacteria to solid surfaces (page 141, 1st column). Lockman et al teach that flagella (H antigen) on the surface of *Salmonella typhimurium* have been characterized as virulence factors that help the bacteria move towards and adhere to the host cells (page 137, 1st column). Lockman et al teach that passive immunization of mice with anti-H antiserum did not protect the animals from a lethal challenge with virulent organisms, although the antiserum inhibited bacterial adherence to intestinal epithelium *in vitro* (page 137, 1st column). Lockman et al teach that nonflagellated strains colonized the intestinal tracts of orally vaccinated mice as well as isogenic flagellated strains yet did not confer equal protection from subsequent lethal challenge by motile *S. typhimurium* (page 137, 2nd column). Lockman et al teach that flagella were necessary for *S. typhimurium* to invade and cause severe disease and the nonflagellated strains were equally proficient at colonization of the murine intestinal tract, but these mutants were deficient in invasion of the reticuloendothelial system (2nd column, page 141). Hackett et al (*The Journal of Infectious Diseases, Vol. 157, January 1988)* teach protective and nonprotective strains of *Salmonella*. Hackett et al teach that when mice were fed strains of *Salmonella* a limited infection in the Peyer's patches was established and generated resistance to subsequent challenge with virulent *S. typhimurium* C5 and the these five strains of *Salmonella* are termed "protective" because they did not give rise to bacteremia or colonization in the liver or spleen (1st column, page 80). Hackett et al teach that also teach eight strains of *Salmonella* and one strain from *E. coli* expressing O-antigens 1,4, 5 and 12 of *S. typhimurium* administered to mice orally that fail to induce resistance to

the virulent *S. typhimurium* C5 challenge, these strains are termed "nonprotective" (page 80 in particular, Table 1). Hackett et al teach that *S. typhimurium* C5 and the five protective strains expressed one to two prominent cell envelope polypeptides of 50-55 kDa which were not expressed by the nonprotective strains with the exception of *S. derby*. Hackett et al teach that these polypeptides were loosely associated with the cell envelope and there molecular mass values of about 50 to 55 kDa suggesting that they might be composed of flagellin. Hackett et al confirmed that six of the "protective" strains in which polypeptides were detected contained flagellin either (the H-1i antigen or the H-2 1 antigen) (page 80 and figures 1B and C). Hackett et al teach that *S. typhimurium* C5 and all five of protective strains examined expressed high levels of flagella whereas only one of the eight nonprotective did so (page 81). Hackett et al suggests a correlation between the expression of high levels of flagellin by a *Salmonella* strain, its ability to colonize mice when given orally and its ability to protect against subsequent oral *S. typhimurium* C5 challenge (page 81). Hackett et al determined that there is a correlation between protection and colonization by administering orally to mice flagella-positive (fla+) and flagella-negative (fla-) strains of *Salmonella*. Hackett et al teach that the fla- colonized the Peyer's patch as well as the fla+ strains and when give orally no strain colonized the spleens of infected mice (1st column, page 82). Hackett et al teach that there is a correlation between flagella expression and protective efficacy because mice immunized with fla+ strains showed lower numbers of challenge bacteria in the spleen than did mice immunized with the fla- strains, a result agreeing with the greater protective effects of immunization with the fla+ strains. Hackett et al

teach that the levels of challenge strain in the spleens of the immunized mice were similar to three days postinfection, but mice immunized with fla+ strains eliminated the challenge whereas the mice immunized with fla- strains did not (pages 81-82). Hackett et al teach that it is uncertain whether the relative inefficacy of the fla- vaccines results from their inability to elicit immunity to flagella or from their inability (compared with fla+ strains) to induce immune responses to a wider range of bacterial antigens (2nd column, page 83). Hackett et al teach that flagella promote the intracellular survival of *Salmonella* after ingestion by macrophages and therefore fla+ and fla- bacteria are perhaps "processed" differently by these cells because macrophages can function as antigen presenting cells and this might lead to qualitative and quantitative differences in immune response (2nd column, page 83). Wahdan et al *(Bull World Health Organization, vol. 52, 1975)* teach a nonmotile mutant of *Salmonella typhi* Ty2 which produces high levels of Vi and O titers but is devoid of the flagellar antigen (does not induce formation of H antibody) (page 69). Wahdan et al teach that the nonmotile vaccine was produced with strain TNM1 (page 69). Wahdan et al teach that the TNM1 vaccine is identical to other *S. typhi* whole cell vaccines prepared with Ty2 except that it is devoid of the H antigen and therefore does not interfere with the Widal test for H antibody (page 71). Wahdan et al teach that the TNM1 vaccine did not provide protection. Wahdan et al teach that there is a correlation between the H antibody and protection and suggests that it seems more probable that a property other than the synthesis of flagellar antigen determines immunogenicity and it is absent from the TNM1 non-motile mutant (page 72).

The vaccine composition "is in live attenuated form". The specification teaches that the claimed vaccine compositions can be in a live attenuated form or inactivated (page 11). The specification teaches that the development of live attenuated vaccines in general is difficult and time consuming. The specification teaches that fine-tuning of the degree of attenuation is complex because high virulence causes disease and low virulence induces insufficient protection (page 11). The specification teaches that removal of the flagellin gene does not significantly change the level of attenuation (page 11). Lockman et al *(Infection and Immunity, January 1990, p. 137-143)* teach that the role of the flaF25 mutation in the attenuation of *S. typhimurium* is unclear. The flaF25 mutation was correlated with flagellar biosynthesis and was originally described as a deletion of unknown size within the flaF gene cluster but was subsequently report as a deletion of genes flaFI through flaFV. The flaF25 mutation had been reported to involve not only some of the genes encoding the biosynthesis of flagella but extended into to a previously undescribed virulence gene(s)(2nd column, page 137).

The prior art has taught that flagella (H antigen) enable bacterial cells to move chemotactically in response to stimuli and there is evidence that these organelles function in the attachment of certain bacteria to solid surfaces. The prior art has taught flagella have been characterized as virulence factors. The prior art has taught that fla+ strains express one to two proteins of about 50 to 55 kDa which correspond to the H-1i antigen and the H-2 1 antigen (i.e. flagellin) with the exception of *S. derby*. There is a correlation between high level of flagella, colonization and protection regarding protective *Salmonella* strains. The prior art teaches that although fla+ and fla- strains

equally colonize the Peyers patch, the fla+ strains eliminated challenge bacteria whereas the fla- strains did not. The prior art teaches that live oral *Salmonella* vaccines comprising fla+ strains have been found to be superior against *S. typhimurium* C5 infection in mice. The prior art teaches that fla+ strains may be superior vaccines because macrophages may process bacteria cells that contain flagella differently than those that do not since the prior art has taught that macrophages can function as antigen presenting cells. The prior art has taught that there is a correlation between protection and the H antigen since a nonmotile mutant (lacking the H antigen) of Salmonella typhi did not protect patients against typhoid fever. The prior also teaches that a property other than the synthesis of flagellar antigen determines immunogenicity and it is absent from the TNM1 non-motile mutant. The prior art that the role of attenuation to produce *Salmonella* nonflagelated mutants is unclear.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

In view of the teachings of the specification (or the lack thereof) and the teachings of the prior art there is lack of enablement for the a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritditis, cholerasuis, dublin, abortus-ovi, abortus-equi, derby, habar,*

heidelberg, agona, arizonae, typhi or paratyphi A and B, wherein said mutated bacterium lacking flagellin and the said vaccine composition is protective. The specification has shown that the vaccines comprising mutated bacterium lacking flagellin from *S. typhimurium* STMP are protective. It is determine that there are limited working examples commensurate in scope with the instant claims and there is limited guidance provided in the specification as to how to make and use vaccine compositions that comprise a mutated from any *Salmonella* bacterium (other than STM2000) lacking flagellin that are protective against Salmonellosis. The skilled artisan is forced into undue experimentation to practice (make and use) the invention as is broadly claimed because the prior has taught that many strains of fla- are not protective, do not confer protection from subsequent challenge by motile *Salmonella* bacteria and that mutations such as the flaF25 mutation in the attenuation of *Salmonella* bacterium is unclear.

Status of Claims

4. No claims are allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

6. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
June 27, 2003

PATRICIA A. DUFFY
PRIMARY EXAMINER